

Amyotrophic Lateral Sclerosis: An overview

K. Sandhiya¹, Dr. Lavanya Babu^{2*}, R. Swathi¹, S. Shakthi Sree¹, Dr. R. Srinivasan³

¹Undergraduate Students, Faculty of Pharmacy, Bharath Institute of Higher Education and Research, 173, Agaram Road, Selaiyur, Tambaram, Chennai – 600073

²Professor, Department of Pharmacognosy, Bharath Institute of Higher Education and Research 173, Agaram Road, Selaiyur, Tambaram, Chennai – 600073

³Dean & Professor, Department of Pharmaceutical Chemistry and Analysis, Bharath Institute of Higher Education and Research, 173, Agaram Road, Selaiyur, Tambaram, Chennai – 600073

Corresponding Author: Dr. Lavanya Babu

DOI: 10.67224/ioasdjmps.2025.v02i03.001

Professor, Department of Pharmacognosy, Bharath Institute of Higher Education and Research 173, Agaram Road, Selaiyur, Tambaram, Chennai – 600073.

ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease which characterized by pathogenic protein aggregates that correlate with the progressive degeneration of neurons and the loss of behavioral functions. It is now more often recognized as Lou Gehrig's disease in the US. ALS is an uncommon disease; diagnosis is often delayed because more prevalent conditions are taken into consideration before ALS. ALS has a about 1 in 350 lifetime risk. The genes responsible for 10% of sporadic ALS and two thirds of familial A physiology and causation are still mostly unclear. A common pathogenic characteristic of both familial and sporadic ALS is toxicity, which can also result from aggregation of both wild-type and mutant proteins. The goal of ALS treatment is to maximize quality of life and use disease-modifying treatments because the condition is still incurable. This review outline about the ALS disease and discuss the status of ALS in human neurons which may improve care and outcome for ALS patients

Keywords: Amyotrophic lateral sclerosis (ALS), neurons, sporadic Amyotrophic lateral sclerosis (SALS), familial Amyotrophic lateral sclerosis (FALS).

Review Article

Article History

Received: 07-03-2025

Accepted: 09-05-2025

Published: 16-07-2025

Copyright © 2025 The Author(s): This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY-NC) which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited.



INTRODUCTION

A terminal neurodegenerative illness, amyotrophic lateral sclerosis (ALS) causes the gradual degradation of both upper and lower motor neurons that typically regulate voluntary muscular contraction [1]. ALS-affected neural system components that result in increasing symptoms in the body's skeletal muscles [2]. A degenerative, late-onset motor neuron disease. The disease's name comes from Charcot's observation in the lateral portions of the spinal cord of a distinct "myelin pallor," which represents the degeneration and loss of the axons of upper motor neurons as they descend from the brain to connect directly or indirectly onto the lower motor neurons within the spinal cord. The disease's main clinical features include the premature degeneration and death of upper and lower motor neurons, which causes fatal paralysis. Midlife is when the disease first appears, and it usually lasts one to five years. Originally named as Charcot's sclerosis, it is now more often recognized as Lou Gehrig's disease in the US. With a lifetime risk of roughly 1 in 1000, ALS's impact is underestimated when

incidence and prevalence are taken into account [3, 4, 5]. The main neuropathological characteristics of ALS include reactive gliosis, which is the hypertrophy of glial cells in the motor cortex and spinal cord in the areas of degeneration, loss of Betz cells (large pyramidal cell neurons) in the primary motor cortex, degeneration of the lateral corticospinal tracts, that store the axons projecting from the primary motor cortex to the motor neurons, and extensive loss of lower motor neurons from the anterior horns of the spinal cord and brainstem [6, 7, 8]. When motor neurons in ALS gradually deteriorate, they ultimately die. Indeed, ALS is linked to a complex pathophysiology that includes endoplasmic reticulum stress, mitochondrial dysfunction, microglial activation, excitotoxicity, peripheral inflammation, neuron loss, muscle atrophy, oxidative stress, and synaptic remodeling [9, 10].

SYMPTOMS OF ALS

During its early stages, amyotrophic lateral sclerosis (ALS), a deadly neurodegenerative disease of

the central nervous system, can be hard to diagnose. ALS is an uncommon disease, diagnosis is often delayed because more prevalent conditions are taken into consideration before ALS. ALS has a about 1 in 350 lifetime risk, while the prevalence is decreased by a short life expectancy [11]. The lifetime accumulation of environmental exposures, including lifestyle choices, is known as the ALS exposome. Several case-control studies have investigated how environmental risk variables related to employment, housing, and leisure affect the risk of ALS [12]. These cell populations' dysfunction and death cause gradual muscle weakness and atrophy, which eventually results in paralysis and death three to five years after the disease first manifests [13].

CAUSES OF ALS

About 10% of cases of ALS are familial, and they might be X-linked, autosomal dominant, or autosomal recessive. The great majority of ALS cases are categorized as sporadic, meaning that there is no known history of another family member having either ALS or frontotemporal dementia. Because of advancements in

sequencing technologies, the list of genes that cause ALS has expanded significantly to over 40. The genes responsible for 10% of sporadic ALS and two thirds of familial A physiology and causation are still mostly unclear. Sporadic ALS, which makes up the bulk of ALS cases, is also believed to have a genetic component to its pathophysiology. Nevertheless, there hasn't been much progress in identifying gene abnormalities in SALS cases lately. Numerous organizations have published information on gene variations and correlation analyses discovered in people with sporadic ALS. Only a small percentage of all cases are explained by these studies that relate specific genetic variations to SALS. This suggests that there is a complex pattern of inheritance with extremely low penetrance, a high degree of heterogeneity, and/or the presence of environmental variables that cause ALS. FALS and SALS are not clinically different, with the exception of a small number of familial ALS cases when other neurodegenerative illnesses may occur concurrently. But there are a few small but intriguing variations. Compared to sporadic ALS, which typically manifests at age 56, family instances typically manifest around age 46 [14].

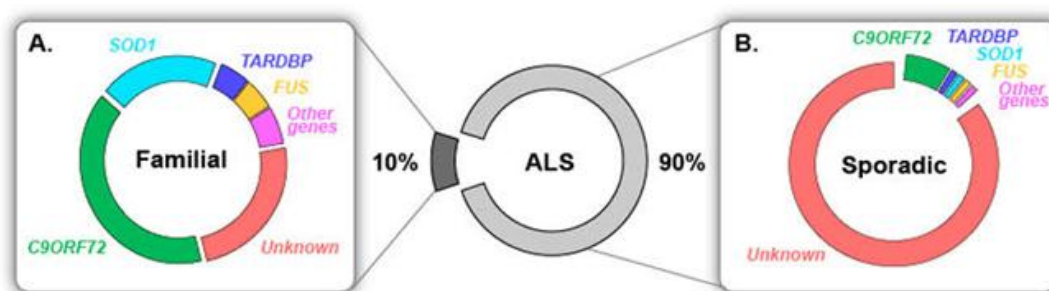


Figure 1

FALS has a male to female ratio of 1:1, whereas SALS has an unexplained male preponderance of 1.5:1 that is recorded globally, albeit this ratio tends to decline and approaches 1:1 beyond age 70 [15]. Family FALS was first identified as having a genetic etiology related to a mutation in Cu–Zn superoxide dismutase 1 (SOD1). Citation 4 Most SOD1 mutations are AD, have a highly penetrant inheritance pattern, and are mostly linked to ALS that develops in the limb [16].

PATHOPHYSIOLOGY OF ALS

Pathological processes in ALS are caused by toxic gain-of-function or loss-of-function mutations in the roughly 40 ALS genes that are now known to exist. A common pathogenic characteristic of both familial and sporadic ALS is toxicity, which can also result from aggregation of both wild-type and mutant proteins [17]. Impaired RNA metabolism, altered proteostasis/autophagy, cytoskeletal/trafficking abnormalities, and mitochondrial dysfunction are the four main categories into which pathophysiological

processes can be generally divided [18]. Numerous studies have examined and emphasized the significance of various cell types, including as microglia [19], astrocytes [20], oligodendrocytes [21], muscles [22], Schwann cells [23], the neuromuscular junction (NMJ) [24], and the gut microbiota [25], in the pathophysiological basis of ALS. A surprising finding given the impact of undernutrition on energy balance and the defense mechanisms to reduce energy waste is that over 60% of patients with familial and sporadic ALS have higher resting and non-resting energy consumption, according to various studies [26, 27, 28]. According to a study with a sizable ALS patient population, being physically active was linked to a higher chance of developing ALS [29, 30]. According to the dying forward theory, which has been proposed as the basis for ALS, corticomotoneuronal hyperexcitability mediates neuronal degeneration by a transsynaptic anterograde mechanism [31]. It is crucial to note that some have proposed that cortical hyperexcitability is a compensatory reaction to degeneration of spinal motoneuron [32].

Amyotrophic Lateral Sclerosis (ALS)

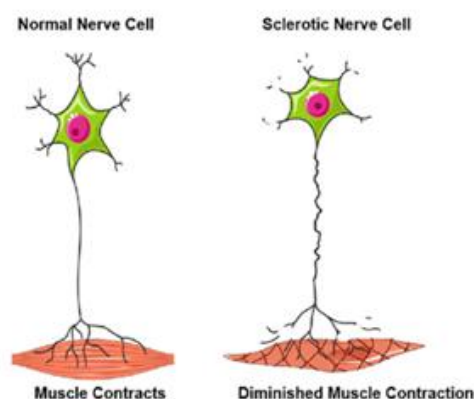


Figure:2

DIAGNOSIS

The diagnosis of ALS is clinical, in view of the set of experiences and actual assessment showing moderate upper and lower engine neuron brokenness. It is typically upheld by electrophysiological review and neuroimaging and research center tests to reject mimickers. The El Escorial rules have been created to normalize the analysis for clinical exploration [33]. Familial ALS is more easily identified when there is a positive family history; however, familial ALS may present as sporadic disease on account of incomplete penetrance or incomplete family history. In the absence of family history, an early age of onset, atypical rapid or slow disease progression, pure lower motor neuron presentation or the presence of dementia may alert to a familial etiology [34]. The disease starts with limb weakness in about two-thirds of patients, often preceded by cramps, and with bulbar weakness causing dysarthria and dysphagia in the remaining one-third. In rare instances, cognitive impairment, behavioral disturbances or early respiratory failure can be the initial manifestation of ALS. The characteristic combination of upper and lower motor neuron dysfunction is usually evident on neurological examination with the presence of weakness, atrophy and fasciculations together with hyper-reflexia and increased tone in the same motor segment and not infrequently an extensor response to plantar stimulation [35].

TREATMENT

The most common known ALS risk gene, C9 or f72, lowers the onset age in males compared to females [36]. Genetics also plays a part; heritability is higher in mother-daughter pairs [11] and ALS results from complex interactions between age, sex, and genetics, which has implications for preclinical and clinical research as well as clinical trials [37]. The goal of ALS treatment is to maximize quality of life and use disease-modifying treatments because the condition is still incurable. According to evidence-based and expert consensus guidelines for managing ALS published by the American Academy of Neurology, the European

Federation of Neurological Societies, the National Institute for Health and Care Excellence (NICE) in the United Kingdom [38] and ALS Canada [39] supportive multidisciplinary care increases ALS patients' quality of life and survival [40]. Deciphering pathogenic pathways and identifying disease-causing molecules are necessary to develop therapeutic approaches for treating ALS. Numerous potential external factors have been studied, such as the usage of pesticides, viruses, cyanobacterial toxins, magnetic fields, heavy metals, a medical history, and lifestyle decisions [41,42]. To yet, however, a distinct environmental risk factor has not been discovered. More than 30 genes that cause ALS and frontotemporal dementia (FTD) have been found to have mutations since the original discovery of superoxide dismutase 1 (SOD1) as an ALS causative gene in 1993 [43]. This has been made possible by extensive research efforts and sophisticated genetic techniques [44, 45, 46, 47]. It has also been demonstrated that 147 distinct gene mutations in several pathways contribute to the pathophysiology of ALS [48,49].

CONCLUSION

ALS remains difficult to diagnose and manage. This is due to heterogeneous ALS presentation and phenotype, and symptom and sign overlap with other illnesses. Earlier on in the diagnostic process, physicians should refer patients presenting with progressive dysarthria, dysphagia, limb weakness, or respiratory failure to a neurologist.

It conclude that ALS is a neurodegenerative disease which effect the neurons and this condition is still incurable . It genetically transmitted disease from one generation to another generation. Recently research at Duke University found that a change in the IGFBP7 gene is more common in people who have experienced a reversal of MND. This change may make motor neurons more resistant to the mechanism that lead to motor death. We anticipate that these research efforts will translate into improved outcomes for current and future patients with ALS.

REFERENCE

1. Amyotrophic Lateral Sclerosis (ALS) Fact Sheet". National Institute of Neurological Disorders and Stroke. Archived from the original on 5 January 2017. Retrieved 22 October 2020.
2. Masrori P, Van Damme P (October 2020). "Amyotrophic lateral sclerosis: a clinical review". *European Journal of Neurology*. 27 (10): 1918–1929. Doi:10.1111/ene.14393. PMC 7540334. PMID 32526057.
3. J.M. Charcot, A. (1869). Joffroy Deux cas d'atrophie musculaire progressive avec lesion de la substance grise et des faisceaux antero-lateraux de la moelle epiniere Arch. Physiol. Neurol. Path., 2, pp. 744-754
4. Gordon, P. H., Mitsumoto, H., & Hays, A. P. (2003). Amyotrophic lateral sclerosis. *Science of Aging Knowledge Environment*, 2003(35), dn2-dn2.
5. Yoshida, S., Mulder, D. W., Kurland, L. T., Chu, C. P., & Okazaki, H. (1986). Follow-up study on amyotrophic lateral sclerosis in Rochester, Minn., 1925 through 1984. *Neuroepidemiology*, 5(2), 61-70.
6. Abe, K., Fujimura, H., Toyooka, K., Sakoda, S., Yorifuji, S., & Yanagihara, T. (1997). Cognitive function in amyotrophic lateral sclerosis. *Journal of the neurological sciences*, 148(1), 95-100.
7. Al-Sarraj, S., King, A., Troakes, C., Smith, B., Maekawa, S., Bodi, I., ... & Shaw, C. E. (2011). p62 positive, TDP-43 negative, neuronal cytoplasmic and intranuclear inclusions in the cerebellum and hippocampus define the pathology of C9orf72-linked FTLTD and MND/ALS. *Acta neuropathologica*, 122, 691-702.
8. ALS Mutation Database. (2007). The University of Tokyo;(reseq.biosciencedbc.jp/resequence/SearchDisease.do?targetId=1). [Google Scholar]
9. Swinnen, B., & Robberecht, W. (2014). The phenotypic variability of amyotrophic lateral sclerosis. *Nature Reviews Neurology*, 10(11), 661-670. Doi: 10.1038/nrneurol.2014.184.
10. Morgan, S., & Orrell, R. W. (2016). Pathogenesis of amyotrophic lateral sclerosis. *British medical bulletin*, 119(1), 87-97. Doi: 10.1093/bmb/ldw026.
11. Ryan, M., Heverin, M., McLaughlin, R. L., & Hardiman, O. (2019). Lifetime risk and heritability of amyotrophic lateral sclerosis. *JAMA neurology*, 76(11), 1367-1374.
12. Su, F. C., Goutman, S. A., Chernyak, S., Mukherjee, B., Callaghan, B. C., Batterman, S., & Feldman, E. L. (2016). Association of environmental toxins with amyotrophic lateral sclerosis. *JAMA neurology*, 73(7), 803-811.
13. Gregory, J. M., Fagegaltier, D., Phatnani, H., & Harms, M. B. (2020). Genetics of amyotrophic lateral sclerosis. *Current Genetic Medicine Reports*, 8, 121-131.
14. Camu, W., Khoris, J., Moulard, B., Salachas, F., Briolotti, V., Rouleau, G. A., & Meininger, V. (1999). Genetics of familial ALS and consequences for diagnosis. *Journal of the neurological sciences*, 165, S21-S26.
15. Haverkamp, L. J., Appel, V., & Appel, S. H. (1995). Natural history of amyotrophic lateral sclerosis in a database population Validation of a scoring system and a model for survival prediction. *Brain*, 118(3), 707-719.
16. Andersen, P. M. (2006). Amyotrophic lateral sclerosis associated with mutations in the CuZn superoxide dismutase gene. *Current neurology and neuroscience reports*, 6(1), 37-46.
17. Mackenzie, I. R., Rademakers, R., & Neumann, M. (2010). TDP-43 and FUS in amyotrophic lateral sclerosis and frontotemporal dementia. *The Lancet Neurology*, 9(10), 995-1007.
18. Nguyen, H. P., Van Broeckhoven, C., & van der Zee, J. (2018). ALS genes in the genomic era and their implications for FTD. *Trends in Genetics*, 34(6), 404-423.
19. Wang, M. J., Kang, L., Wang, Y. Z., Yang, B. R., Zhang, C., Lu, Y. F., & Kang, L. (2022). Microglia in motor neuron disease: Signaling evidence from last 10 years. *Developmental Neurobiology*, 82(7-8), 625-638.
20. Almad, A. A., Taga, A., Joseph, J., Gross, S. K., Welsh, C., Patankar, A., ... & Maragakis, N. J. (2022). Cx43 hemichannels contribute to astrocyte-mediated toxicity in sporadic and familial ALS. *Proceedings of the National Academy of Sciences*, 119(13), e2107391119.
21. Gong, Z., Ba, L., & Zhang, M. (2022). Dysfunction of the oligodendrocytes in amyotrophic lateral sclerosis. *Journal of Biomedical Research*, 36(5), 336.
22. Badu-Mensah, A., Guo, X., Nimbalkar, S., Cai, Y., & Hickman, J. J. (2022). ALS mutations in both human skeletal muscle and motoneurons differentially affects neuromuscular junction integrity and function. *Biomaterials*, 289, 121752.
23. Harrison, J. M., & Rafuse, V. F. (2020). Muscle fiber-type specific terminal Schwann cell pathology leads to sprouting deficits following partial denervation in SOD1G93A mice. *Neurobiology of Disease*, 145, 105052.
24. Verma S., Khurana S., Vats A., Sahu B., Ganguly N.K., Chakraborti P., Gourie-Devi M., Taneja V. (2022) Neuromuscular Junction Dysfunction in Amyotrophic Lateral Sclerosis. *Mol. Neurobiol.*, 59:1502–1527. Doi: 10.1007/s12035-021-02658-6.
25. Martin, S., Battistini, C., & Sun, J. (2022). A gut feeling in amyotrophic lateral sclerosis: microbiome of mice and men. *Frontiers in cellular and infection microbiology*, 12, 839526.
26. Fayemendy, P., Marin, B., Labrunie, A., Boirie, Y., Walrand, S., Achamrah, N., ... & Jésus, P. (2021). Hypermetabolism is a reality in amyotrophic lateral sclerosis compared to healthy subjects. *Journal of the Neurological Sciences*, 420, 117257.
27. Steyn, F. J., Ioannides, Z. A., Van Eijk, R. P., Heggie, S., Thorpe, K. A., Ceslis, A., ... & Ngo, S.

- T. (2018). Hypermetabolism in ALS is associated with greater functional decline and shorter survival. *Journal of Neurology, Neurosurgery & Psychiatry*, 89(10), 1016-1023.
28. Ferri, A., & Coccurello, R. (2017). What is "Hyper" in the ALS Hypermetabolism?. *Mediators of inflammation*, 2017(1), 7821672.
 29. Harwood, C. A., Westgate, K., Gunstone, S., Brage, S., Wareham, N. J., McDermott, C. J., & Shaw, P. J. (2016). Long-term physical activity: an exogenous risk factor for sporadic amyotrophic lateral sclerosis?. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, 17(5-6), 377-384.
 30. Pupillo, E., Bianchi, E., Vanacore, N., Montalto, C., Ricca, G., Robustelli Della Cuna, F. S., ... & Beghi, E. (2020). Increased risk and early onset of ALS in professional players from Italian Soccer Teams. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, 21(5-6), 403-409.
 31. Eisen, A., Kim, S., & Pant, B. (1992). Amyotrophic lateral sclerosis (ALS): a phylogenetic disease of the corticomotoneuron?. *Muscle & nerve*, 15(2), 219-224.
 32. Zanette, G., Tamburin, S., Manganotti, P., Refatti, N., Forgiione, A., & Rizzuto, N. (2002). Different mechanisms contribute to motor cortex hyperexcitability in amyotrophic lateral sclerosis. *Clinical Neurophysiology*, 113(11), 1688-1697.
 33. Brooks, B. R., Miller, R. G., Swash, M., & Munsat, T. L. (2000). El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotrophic lateral sclerosis and other motor neuron disorders*, 1(5), 293-299.
 34. Appel, S. H., & Rowland, L. P. (2012). Amyotrophic lateral sclerosis, frontotemporal lobar dementia, and p62: a functional convergence?. *Neurology*, 79(15), 1526-1527.
 35. Logroscino, G., Traynor, B. J., Hardiman, O., Couratier, P., Mitchell, J. D., Swinger, R. J., & Beghi, E. (2008). Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues. *Journal of Neurology, Neurosurgery & Psychiatry*, 79(1), 6-11.
 36. Murphy, N. A., Arthur, K. C., Tienari, P. J., Houlden, H., Chiò, A., & Traynor, B. J. (2017). Age-related penetrance of the C9orf72 repeat expansion. *Scientific reports*, 7(1), 2116.
 37. Chiò, A., Moglia, C., Canosa, A., Manera, U., D'Ovidio, F., Vasta, R., ... & Calvo, A. (2020). ALS phenotype is influenced by age, sex, and genetics: a population-based study. *Neurology*, 94(8), e802-e810.
 38. <https://www.nice.org.uk/guidance/ng42>
 39. <https://www.cmaj.ca/content/cmaj/192/46/E1453.full.pdf>.
 40. Klavžar, P., Koritnik, B., Leonardis, L., Dolenc Grošelj, L., Kirbiš, M., Ristić Kovačič, S., ... & Zidar, J. (2020). Improvements in the multidisciplinary care are beneficial for survival in amyotrophic lateral sclerosis (ALS): experience from a tertiary ALS center. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, 21(3-4), 203-208.
 41. Filippini, T., Fiore, M., Tesauro, M., Malagoli, C., Consonni, M., Violi, F., ... & Vinceti, M. (2020). Clinical and lifestyle factors and risk of amyotrophic lateral sclerosis: A population-based case-control study. *International journal of environmental research and public health*, 17(3), 857.
 42. Oggiano, R., Pisano, A., Sabalic, A., Farace, C., Fenu, G., Lintas, S., ... & Madeddu, R. (2021). An overview on amyotrophic lateral sclerosis and cadmium. *Neurological Sciences*, 42, 531-537.
 43. Rosen, D. R., Siddique, T., Patterson, D., Figlewicz, D. A., Sapp, P., Hentati, A., ... & Brown Jr, R. H. (1993). Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. *Nature*, 362(6415), 59-62.
 44. Renton, A. E., Chiò, A., & Traynor, B. J. (2014). State of play in amyotrophic lateral sclerosis genetics. *Nature neuroscience*, 17(1), 17-23.
 45. Ito, D., Hatano, M., & Suzuki, N. (2017). RNA binding proteins and the pathological cascade in ALS/FTD neurodegeneration. *Science Translational Medicine*, 9(415), eaah5436.
 46. Taylor, J. P., Brown Jr, R. H., & Cleveland, D. W. (2016). Decoding ALS: from genes to mechanism. *Nature*, 539(7628), 197-206.
 47. Xue, Y. C., Ng, C. S., Xiang, P., Liu, H., Zhang, K., Mohamud, Y., & Luo, H. (2020). Dysregulation of RNA-binding proteins in amyotrophic lateral sclerosis. *Frontiers in molecular neuroscience*, 13, 78.
 48. Dudman, J., & Qi, X. (2020). Stress granule dysregulation in amyotrophic lateral sclerosis. *Frontiers in cellular neuroscience*, 14, 598517.
 49. Dervishi, I., Gozutok, O., Murnan, K., Gautam, M., Heller, D., Bigio, E., & Ozdinler, P. H. (2018). Protein-protein interactions reveal key canonical pathways, upstream regulators, interactome domains, and novel targets in ALS. *Scientific reports*, 8(1), 1-19.